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Supplemental Statistical Analysis Plan (sSAP)

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1 INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2 SUMMARY OF CHANGES

08-Oct-2021

The document has been updated to align with the amended protocol (033-01). Other changes include:

Section	Description of Change	Rationale
Section 3.5.1 Immunogenicity Analysis Populations	Updated as follows: The FAS population consists of all randomized participants who received all study vaccinations required at the timepoint for the analysis and have at least one serology result at the time point for the analysis.	For further clarification.
Section 3.5.2 Safety Analysis Population	Updated as follows: Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study vaccination for the timepoint of interest. For safety analyses following any dose of PCV, participants vaccinated with PCV at any time point will be included. For safety analyses following each dose of PCV, participants vaccinated with PCV at that dose will be included.	For further clarification.
Section 3.6.1 Statistical Methods for Immunogenicity Analyses	Table 1 p-value was added in the Statistical Method column for the analysis of Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for the 13 shared serotypes	For further clarification.
Section 3.6.1 Statistical Methods for Immunogenicity	The following sentence was added: Reverse cumulative distribution function curves will be provided for the serotype-specific IgG concentrations	To provide additional statistical analysis details / data derivation.

Analyses	and OPA titers for each timepoint.	
Section 3.6.1 Statistical Methods for Immunogenicity Analyses	Added a paragraph and a table (Table 2) to explain how values below the LLOQ or above the ULOQ should be treated in various analyses.	To provide additional statistical analysis details / data derivation.

3 ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 3.2 through 3.12.

Study Design Overview	A Phase 3, Multicenter, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Japanese Infants
Treatment Assignment	Participants will be randomly assigned in a 1:1 ratio to V114 or Prevenar 13™, stratified by age category (2 months, 3 months, 4 to 6 months of age).
Analysis Population	Immunogenicity: Per-Protocol (PP) Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	Immunogenicity: • Anti-PnPs serotype-specific IgG response rates (proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL) at 30 days PD3 • Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for the 13 shared serotypes contained in V114 and Prevenar 13™ Safety: • Proportion of participants with solicited injection-site AEs (swelling, redness/erythema, tenderness/pain, and hard lump/induration) from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™ • Proportion of participants with solicited systemic AEs (irritability, drowsiness/somnolence, appetite lost/decreased appetite, and hives or welts/urticaria) from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™ • Proportion of participants with vaccine-related SAEs from Day 1 through completion of study participation
Statistical Methods for Key Immunogenicity Analyses	The between-group differences (V114 minus Prevenar 13™) in the response rates of anti-PnPs serotype-specific IgG at 30 days PD3, along with corresponding 95% CIs based on the method of Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985] stratified by age category (2 months of age, ≥3 months of age), will be estimated. The Cochran-Mantel-Haenszel weight will be used to obtain stratum-adjusted proportion difference. The lower bound of the 95% CIs will be compared against the pre-specified margin of -0.1 to test the non-inferiority hypotheses. Anti-PnPs serotype-specific IgG concentrations at 30 days PD3 for the 13 shared serotypes in V114 and Prevenar 13™ will be natural log-transformed and analyzed using a linear model with factors for vaccination group and age category. Between-group differences (V114 minus Prevenar 13™) and corresponding 95% CIs will be estimated on the log scale using the model above, and the results will be transformed back to the original scale to obtain the IgG GMC ratios (V114/Prevenar 13™). The lower bound of the 95% CIs will be compared against the pre-specified margin of 0.5 to test the non-inferiority hypotheses.
Statistical Methods for Key Safety Analyses	The analysis of safety endpoints will follow a tiered approach. p-Values (Tier 1 endpoints) for between-group comparisons and 95% CIs (Tier 1 and Tier 2 endpoints) for between-group differences in the percentage of participants with the respective events will be provided. These analyses will be performed using the unstratified Miettinen and Nurminen method.
Interim Analysis	No interim analysis is planned.

Multiplicity	The study will be considered to have met its primary immunogenicity objectives if non-inferiority is demonstrated in the IgG response rates for the 15 serotypes and in the IgG GMCs for the 13 shared serotypes, both at 30 days PD3. Successful achievement of the primary immunogenicity objective requires that all individual serotypes within the hypotheses satisfy the pre-specified non-inferiority criteria at a 1-sided α level of 0.025. This approach will control the 1-sided type I error rate at 0.025, thus no multiplicity adjustment will be required. No multiplicity adjustments will be made for the safety objective.
Sample Size and Power	A total of 660 participants will be randomized in a 1:1 ratio to V114 or Prevenar 13™ to have 300 participants per arm in the PP population at 30 days PD3. The study will have an overall power of ~83% for all the primary hypotheses at a 1-sided α level of 0.025, with the underlying serotype-specific IgG response rates as observed in V114 Protocol 008, as well as the true IgG GMC ratios of 1.0 and the true standard deviation of natural log IgG concentration of 1.1 for all shared serotypes.

3.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an IRT (or equivalent).

3.3 Hypotheses/Estimation

The primary immunogenicity objectives are described below.

Primary endpoints/hypotheses (H1 and H2)

The first primary objective is to compare the response rates of anti-PnPs serotype-specific IgG between V114 and Prevenar 13™ at 30 days PD3. The response rate is defined as the proportion of participants with anti-PnPs serotype-specific IgG responses achieving the threshold value of 0.35 µg/mL. The objective will be assessed via the following non-inferiority hypotheses:

H_0: p_1-p_2 ≤-0.1 versus

H_1: p_1-p_2 >-0.1.

For the 13 shared serotypes contained in V114 and Prevenar 13™, p_1 is the response rate for the V114 group and p_2 is the response rate for the Prevenar 13™ group. The 2 unique

serotypes in V114 will be compared with the shared serotype with the lowest response rate in the Prevenar 13™ group. For the 2 serotypes unique to V114, p_1 is the response rate of the 2 unique serotypes for the V114 group and p_2 is the lowest response rate among all 13 shared serotypes for the Prevenar 13 ™ group. V114 is non-inferior to Prevenar 13™ if the lower bound of the 2-sided 95% CI for the between-group differences (V114 minus Prevenar 13™) is greater than -0.1.

Primary endpoints/hypotheses (H3)

The second primary objective is to compare the anti-PnPs serotype-specific IgG GMCs between V114 and Prevenar 13™ at 30 days PD3 for the 13 shared serotypes contained in V114 and Prevenar 13™. The objective will be assessed via the following non-inferiority hypotheses:

H_0: $GMC_1/GMC_2 \leq 0.5$ versus

H_1: $GMC_1/GMC_2 > 0.5$,

where GMC1 is the anti-PnPs serotype-specific IgG GMCs for the V114 group and GMC2 is the anti-PnPs serotype-specific IgG GMCs for the Prevenar 13™ group. A ratio of 0.5 corresponds to a 2.0-fold decrease of anti-PnPs serotype-specific IgG GMCs in the V114 group as compared with the Prevenar 13™ group. V114 is non-inferior to Prevenar 13™ if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevenar 13™) is greater than 0.5.

3.4 Analysis Endpoints

3.4.1 Immunogenicity Endpoints

The primary immunogenicity endpoints include:

- Proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL (response rate) at 30 days PD3 for the 13 shared serotypes in V114 and Prevenar 13™, and for the 2 serotypes unique to V114
- Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for the 13 shared serotypes in V114 and Prevenar 13™

The secondary immunogenicity endpoints include:

- Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for the 2 serotypes unique to V114
- Anti-PnPs serotype-specific IgG response rates at 30 days PD4
- Anti-PnPs serotype-specific IgG GMCs at 30 days PD4
- Anti-PnPs serotype-specific OPA GMTs at 30 days PD3

- Anti-PnPs serotype-specific OPA GMTs at 30 days PD4
- Anti-PnPs serotype-specific OPA response rates at 30 days PD3
- Anti-PnPs serotype-specific OPA response rates at 30 days PD4

The exploratory endpoints include:

- Anti-PnPs serotype-specific IgG response rates at Predose 4
- Anti-PnPs serotype-specific IgG GMCs at Predose 4
- Anti-PnPs serotype-specific OPA GMTs at Predose 4
- Anti-PnPs serotype-specific OPA response rates at Predose 4

3.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and postvaccination temperature measurements following any vaccination with V114 or Prevenar 13™.

The safety endpoints include:

- Proportion of participants with solicited injection-site AEs (swelling, redness/erythema, tenderness/pain, and hard lump/induration) from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™
- Proportion of participants with solicited systemic AEs (irritability, drowsiness/somnolence, hives or welts/urticaria, and appetite loss/decreased appetite) from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™
- Proportions of participants with the broad AE categories consisting of any AE and a vaccine-related AE from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™
- Proportions of participants with an SAE, a vaccine-related SAE, and discontinuation due to an AE, and death from Day 1 (day of Dose 1) through completion of study participation
- Participants body temperature measured from Day 1 (day of vaccination) through Day 7 following any vaccination with V114 or Prevenar 13™

3.5 Analysis Populations

3.5.1 Immunogenicity Analysis Population

The PP population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s). Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include:

- Failure to receive primary infant series vaccination (V114 or Prevenar 13™ Doses 1, 2, and 3) as per randomization schedule
- Receipt of prohibited medication or prohibited vaccine prior to the first study vaccination

Additional potential deviations that may result in the exclusion from the PP immunogenicity analyses at a particular timepoint include:

- Failure to receive Dose 4 of V114 or Prevenar 13™ according to vaccination schedule required at the timepoint for the analysis
- Failure to receive the scheduled doses of V114 or Prevenar 13™ with the specified intervals / time window (at least 28 days between Doses 1 and 2 and between Doses 2 and 3 [for PD3 and Predose 4 analysis], 12 months to 1 day prior to 16 months of age for Dose 4 [for PD4 analyses])
- Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection
- Collection of blood sample at the timepoint for the analysis outside of the pre specified window (as described in Section 1.3 of the protocol)

The final determination on protocol deviations, and thereby the composition of the PP population, will be made prior to the unblinding of the database.

A supportive analysis using the Full Analysis Set (FAS) population may also be performed for the primary immunogenicity endpoints. The FAS population consists of all randomized participants who received all study vaccinations required at the timepoint for the analysis and have at least one serology result at the time point for the analysis.

Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data.

3.5.2 Safety Analysis Population

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study vaccination for the timepoint of interest.

For safety analyses following any dose of PCV, participants vaccinated with PCV at any time point will be included. For safety analyses following each dose of PCV, participants vaccinated with PCV at that dose will be included. Participants will be included in the group corresponding to the study vaccination they actually received for the analysis of safety data using the APaT population. This will be the group to which they are randomized except for participants who take incorrect study vaccination; such participants will be included in the vaccination group corresponding to the study vaccination actually received. Safety parameters for cross-treated participants (ie, those who received vaccinations of both V114 and Prevenar 13™) will be summarized separately.

At least 1 temperature measurement obtained after study intervention is required for inclusion in the analysis of temperature.

3.6 Statistical Methods

Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

3.6.1 Statistical Methods for Immunogenicity Analyses

The analyses will be conducted for each of the 15 pneumococcal serotypes in V114 separately.

The between-group differences (V114 minus Prevenar 13™) in the response rates of anti-PnPs serotype-specific IgG at 30 days PD3, along with corresponding 95% CIs based on the method of Miettinen and Nurminen stratified by age category (2 months of age, ≥3 months of age), will be estimated. The Cochran-Mantel-Haenszel weight will be used to obtain stratum-adjusted proportion difference. The lower bound of the 95% CIs will be compared against the pre-specified margin of -0.1 to test the non-inferiority hypotheses. Other response rate analyses in immunogenicity endpoints will be performed using the same model as above. Note that the strata of 3 months of age and 4 to 6 months of age will be combined into a single stratum for the purpose of statistical analysis as the number of participants in the 4 to 6 months of age is anticipated to be very small.

Anti-PnPs serotype-specific IgG concentrations at 30 days PD3 for the 13 shared serotypes in V114 and Prevenar 13™ will be natural log-transformed and analyzed using a linear model with factors for vaccination group and age category. Between-group differences (V114 minus Prevenar 13™) and corresponding 95% CIs will be estimated on the log scale using the model above, and the results will be transformed back to the original scale to obtain the IgG GMC ratios (V114/Prevenar 13™). The lower bound of the 95% CIs will be compared against the pre-specified margin of 0.5 to test the non-inferiority hypotheses. The same model will be used to analyze IgG concentrations at 30 days PD3 for the 2 serotypes unique to V114, IgG concentrations at other timepoints, as well as OPA titers.

[Table 1] Summarizes key immunogenicity analyses.

Table 1 Analysis Strategy for Key Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Anti-PnPs serotype-specific IgG response rates at 30 days PD3	P	Stratified Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for the 13 shared serotypes	P	Linear model (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Secondary				
Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for the 2 unique serotypes	P	Linear model (estimate, 95% CI)	PP	Missing data will not be imputed
Anti-PnPs serotype-specific IgG response rates at 30 days PD4	P	Stratified Miettinen and Nurminen (estimate, 95% CI)	PP	Missing data will not be imputed
Anti-PnPs serotype-specific IgG GMCs at 30 days PD4	P	Linear model (estimate, 95% CI)	PP	Missing data will not be imputed
Anti-PnPs serotype-specific OPA GMTs at: • 30 days PD3 • 30 days PD4	P	Linear model (estimate, 95% CI)	PP	Missing data will not be imputed
Anti-PnPs serotype-specific OPA response rates at: • 30 days PD3 • 30 days PD4	P	Stratified Miettinen and Nurminen (estimate, 95% CI)	PP	Missing data will not be imputed
PnPs = pneumococcal polysaccharide, IgG = immunoglobulin G, PD = postdose, PP = Per-Protocol, FAS = Full Analysis Set, CI = confidence interval, OPA = opsonophagocytic activity † P = primary approach, S = supportive approach				

Reverse cumulative distribution function curves will be provided for the serotype-specific IgG concentrations and OPA titers for each timepoint.

The detectable ranges for OPA and IgG responses differ across serotypes. The limits of quantitation define the range of responses over which the assays provide precise and accurate measurements. Table 2 gives the limits of quantitation defined for each serotype for OPA and IgG responses. For responses smaller than the lower limit of quantitation (LLOQ), half of the LLOQ is used for analysis when calculating the OPA GMTs and IgG GMCs, and in the graphical displays of the Reverse Cumulative Distribution Curves for OPA titers and IgG concentrations. For OPA and IgG responses that are larger than the upper limit of quantitation (ULOQ), a value equal to ULOQ + 1 is used for analysis.

Table 2 Limits of Quantitation for OPA and IgG Serotype-specific Responses

	OPA		IgG	
Serotype	**LLOQ (1/dil)**	**ULOQ (1/dil)**	**LLOQ (µg/mL)**	**ULOQ (µg/mL)**
1	9	30,213	0.05	850
3	19	30,564	0.05	145
4	34	137,160	0.05	173
5	27	119,016	0.1	368
6A	232	210,600	0.05	393
6B	40	105,840	0.05	341
7F	61	251,235	0.05	830
9V	151	224,316	0.05	644
14	62	281,637	0.05	1,520
18C	115	445,230	0.05	730
19A	31	128,304	0.05	1,387
19F	113	158,841	0.05	1,461
22F	15	229,338	0.05	1,054
23F	55	251,829	0.05	595
33F	20	399,600	0.05	883

IgG = immunoglobulin G; LLOQ = lower limit of quantitation; OPA= opsonophagocytic activity; ULOQ = upper limit of quantitation.

3.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and postvaccination temperature measurements. Additional summaries on key safety parameters will also be provided following each vaccination.

The analysis of safety results will follow a tiered approach ([Table 3]). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and other safety parameters are either pre-specified as “Tier 1” endpoints or will be classified as belonging to “Tier 2” or “Tier 3” based on the number of participants with events.

Tier 1 Events

Safety parameters or AEs of special interest that are identified *a priori* constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs to be provided for between-group differences in the proportion of participants with events. These analyses will be performed using the unstratified Miettinen and Nurminen method. These p-values and CIs should be regarded as helpful descriptive

measures to be used in review, not formal methods for assessing the statistical significance of the between-group differences. For this protocol, solicited injection-site AEs (redness/erythema, swelling, hard lump/induration, and tenderness/pain) from Day 1 through Day 14 postvaccination and solicited systemic AEs (irritability, drowsiness/somnolence, hives or welts/urticaria, and appetite loss/decreased appetite) from Day 1 through Day 14 postvaccination are considered Tier 1 events.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events (also via the unstratified Miettinen and Nurminen method).

In this study, membership in Tier 2 requires that at least 4 participants in any vaccination group exhibit the event. The threshold of at least 4 participants was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 participants with events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences.

In addition to individual events that occur in at least 4 participants in any treatment group, the broad AE categories consisting of the proportion of participants with any AE, a vaccine-related AE, an SAE, a vaccine-related SAE, discontinuation due to an AE, and death will be considered Tier 2 endpoints. The proportion of participants with maximum temperature measurements meeting particular points (≥37.5 °C, ≥38.0 °C, ≥39.0 °C, ≥40.0 °C) will also be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Medical device incidents due to syringe, if any, will be listed.

Table 3 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Between-Group Comparison	Descriptive Statistics
Tier 1	Injection-site redness/erythema (Days 1 to 14)	X	X	X
	Injection-site swelling (Days 1 to 14)			
	Injection-site tenderness/pain (Days 1 to 14)			
	Injection-site hard lump/induration (Days 1 to 14)			
	Irritability (Days 1 to 14)			
	Drowsiness/somnolence (Days 1 to 14)			
	Hives or welts/urticaria (Days 1 to 14)			
	Appetite loss/decreased appetite (Days 1 to 14)			
Tier 2	Any AE†		X	X
	Any Vaccine-related AE†			
	Any SAE†			
	Any Vaccine-related SAE†			
	Discontinuation due to AE†			
	Death†			
	Maximum temperature measurements meeting cut points (≥37.5 °C, ≥38.0 °C, ≥39.0 °C, ≥40.0 °C; Days 1 to 7)			
	Specific AEs by SOC and PT‡ (incidence ≥4 participants in at least one of the vaccination groups)			
Tier 3	Specific AEs by SOC and PT‡ (incidence <4 participants in all of the vaccination groups)			X

AE = adverse event; CI = confidence interval; PT = preferred term; SAE = serious adverse event; SOC = system organ class; X = results will be provided.
† These endpoints are broad adverse event categories. For example, descriptive statistics for the safety endpoint of "Any AE" will provide the number and percentage of participants with at least one AE.
‡ Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier 2 endpoints.

3.6.3 Summary of Baseline Characteristics

The comparability of the vaccination groups for each relevant demographic and baseline characteristic will be assessed using summary tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, gender, birth weight, and gestational age), baseline characteristics, prior and concomitant vaccinations and therapies will be summarized by vaccination group either by descriptive statistics or categorical tables.

3.7 Interim Analyses

No interim analysis is planned for the study.

3.8 Multiplicity

The study will be considered to have met its primary immunogenicity objective if non-inferiority is demonstrated in the IgG response rates for the 15 serotypes and in the IgG GMCs for the 13 shared serotypes, both at 30 days PD3. Successful achievement of the primary immunogenicity objective requires that all individual serotypes within the hypotheses satisfy the pre-specified non-inferiority criteria at a 1-sided α level of 0.025. This approach will control the 1-sided type I error rate at 0.025, thus no multiplicity adjustment will be required.

No multiplicity adjustments will be made for the safety objective.

3.9 Sample Size and Power Calculations

3.9.1 Sample Size and Power for Immunogenicity Analyses

A total of 660 participants will be randomized in a 1:1 ratio to V114 or Prevenar 13™ to have 300 participants per arm in the PP population at 30 days PD3 (~90% evaluability rate). The study will have an overall power of ~83% for all the primary hypotheses at a 1-sided α level of 0.025. The power calculations for the individual hypotheses are provided below.

Primary endpoints/hypotheses (H1 and H2)

The study will have a power of ~83% at a 1-sided α level of 0.025 to demonstrate that V114 is non-inferior to Prevenar 13™ for the 13 shared serotypes and the 2 unique serotypes in the anti-PnP serotype-specific IgG response rates at 30 days PD3. The underlying serotype-specific response rates are based on the results from V114 Protocol 008 (safety and immunogenicity of two different lots of V114 were evaluated; Lot 1 and Lot 2 pooled for V114), as listed in [Table 4] below.

Table 4 Assumptions of the True Response Rates at 30 Days PD3

Serotype	True Response Rate	
	V114	Prevenar 13™
Prevenar 13™ Types		
1	0.972	0.969
3	0.951	0.718
4	0.976	0.951
5	0.960	0.966
6A	0.931	0.962
6B	0.914	0.914
7F	0.995	0.990
9V	0.975	0.958
14	0.984	0.972
18C	0.975	0.955
19A	0.987	0.986
19F	0.995	0.997
23F	0.936	0.907
Non-Prevenar 13™ Types		
22F	0.987	0.907[†]
33F	0.889	0.907[†]

[†] Serotype 23F; Based on Phase 2 data, serotype 3 had the lowest response rate for PCV13, however, for the purpose of power calculation, the serotype with the next lowest response rate, 23F, was used.

Primary endpoints/hypotheses (H3)

This study will have a power of >99% at a 1-sided α level of 0.025 to demonstrate V114 is noninferior to Prevenar 13™ for the 13 shared serotypes based on the anti-PnP serotype-specific IgG GMCs at 30 days PD3. The power calculations are based on the true IgG GMC ratio of 1.0 and the true standard deviation of natural log IgG concentration of 1.1 for all shared serotypes.

3.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least 1 SAE in this study depends on the number of participants vaccinated and the underlying incidence of participants with an SAE in the study population. Calculations below assume that 100% of the randomized participants will be evaluable for safety analyses. There is an 80% chance of observing at least one SAE among 330 participants in each of the V114 group and Prevenar 13™ group if the underlying incidence of an SAE is approximately 0.49% (1 of every 206 participants receiving the vaccine). There is a 50% chance of observing at least one SAE among 330 participants in each of the V114 group and Prevenar 13™ group if the underlying incidence of an SAE is approximately 0.21% (1 of every 477 participants receiving the vaccine). If no SAEs are observed among 330 participants in each of the V114 group and Prevenar 13™ group, this

study will provide 97.5% confidence that the underlying percentage of participants with an SAE is approximately <1.1% (one in every 90 participants).

[Table 5] summarizes the percentage point differences between the 2 vaccination groups that could be detected with ~80% probability for a variety of hypothetical underlying incidences of an adverse event. These calculations assume 330 participants in each group and are based on a 2-sided 5% alpha level. The calculations are based on an asymptotic method proposed by Farrington and Manning [Farrington, C. P. 1990]; no multiplicity adjustments were made.

Table 5 Differences in Incidence of Adverse Events Between the 2 Vaccination Groups That Can be Detected With an ~80% Probability (Assuming 2-sided 5% Alpha Level With 330 Participants in Each Group)

Incidence of Adverse Event		**Risk Difference**
V114 (%) N=330	**Prevenar 13™ (%) N=330**	**Percentage Points**
2.6	0.1	2.5
6.4	2.0	4.4
10.9	5.0	5.9
17.5	10.0	7.5
23.6	15.0	8.6
29.4	20.0	9.4
40.4	30.0	10.4
Incidences presented here are hypothetical and do not represent actual adverse experiences in either group. Based on an asymptotic method proposed by Farrington and Manning [Farrington, C. P. 1990]		

3.10 Subgroup Analyses

The IgG response rates and IgG GMCs at 30 days PD3 will be analyzed separately by age category (2 months of age, ≥3 months of age; 2 months of age, 3 months of age, 4 to 6 months of age). The IgG response rates will be analyzed using the unstratified Miettinen and Nurminen method, and IgG GMCs will be analyzed using a linear model with a term for vaccination group.

3.11 Compliance (Medication Adherence)

The number and proportion of randomized participants receiving each vaccination will be summarized.

3.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of randomized participants administered V114 or Prevenar 13™.

4 REFERENCES

[Farrington, C. P. 1990]	Farrington CP, Manning G. Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk. Stat Med Vol. 9,1447-1454 (1990)	04FS6L
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	03QCDT